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Division of Dockets Management (HFA - 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
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Docket Number 2004D-0459

Re: Draft Guidance for Industry on Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling

Reference is made to the Agency's request for comments on the draft guidance, *Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling.* Eli Lilly and Company (Lilly), as a global research-based pharmaceutical company, is committed to the development of innovative medications for patients and appreciates the opportunity to provide comments on the proposed guidance.

General Comments

This Draft Guidance provides considerable analysis around "how" to conduct pharmacokinetic (PK) studies during pregnancy but relatively little analysis of the issue of "whether" a PK study during pregnancy should be conducted for a particular compound. Despite this limited analysis, the Draft Guidance proceeds to recommend that a PK study in pregnancy be conducted in four potentially broad situations (lines 156-166). Procedurally, Lilly is concerned that any FDA position on the necessity of such studies for populations to whom the manufacturer does not seek authorization to market is inappropriate for introduction in this Draft Guidance. Substantively, Lilly believes that much greater consideration needs to be given to the relative merits and risks of, and alternatives to, such PK studies than is presented in this Draft Guidance. Accordingly, Lilly recommends that the Guidance be modified to remove the blanket recommendation of conducting PK studies in pregnant women in the four situations set out in lines 156-166 and to either focus exclusively on the issue of "how" to conduct such studies or to restrict the discussion of "whether" to conduct studies to an introduction of the issues and factors one might consider in a given situation.

Lilly believes that there must be a greater emphasis on assessing for a specific drug the need for such PK data and all the alternative sources of information other than conducting PK studies during pregnancy. The fact that few PK studies have been conducted in pregnant women does not support recommending that such studies be conducted for the majority of therapeutics and solely for the interest of science (contrary to Guideline for Good Clinical Practice, Section 2.3). Specifically, any discussion in the Guidance should align with the following initial considerations:

1. Assess the rationale and known PK and pharmacodynamics properties of the drug anticipated to be used during pregnancy,

    a. The analysis of need for a PK study in pregnancy should begin with review of nonclinical studies to ascertain any signals that require special consideration.

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b. The assessment should include a theoretical discussion of how physiologic changes known to occur in pregnancy might have an impact on the PK/PD and safety in pregnancy.

c. Part of this assessment needs to include consideration of a meaningful impact on the clinical drug use in pregnant patients. If the change in PK or PD would need to be extremely large, then performing specific PK/PD studies in a pregnant population may not be justifiable or may point to limiting the study to a much simpler "confirm" design.

2. Consider conducting PK/PD studies in non-pregnant women to evaluate any unknown potential PK effects useful for providing dosing modifications in pregnant women.

3. Consider the power of PK/PD modeling to determine possible dose adjustments to achieve clinically meaningful outcomes in women who become pregnant.

4. Only after the above assessment, if there are no satisfactory alternatives, should the discussion turn to the possibility of adequately designed studies that will result in clinically meaningful outcomes.

A part of each of the above discussions needs to include a thorough benefit-to-risk analysis. The guidance document provides a limited discussion regarding the issues of ethics and of risk. Prior to reaching a conclusion as to the appropriateness of undertaking PK research in pregnant women, there should be a clear assessment as to what are the potential risk to the mother and the unborn child, what is known about the drug's disposition and effects in non-pregnant adults, what are the theoretical or possible effects of pregnancy on these parameters, and what are the key PK, PD and safety issues to be addressed in the research plan. This background information is needed to provide the framework for developing an appropriate research plan, the implementation of which provides informative results regarding dosing in pregnancy in as safe and ethical manner as is possible.

Finally, while Lilly recognizes the value of data derived from controlled clinical studies, conducting such PK studies in pregnant women present considerable practical challenges. The actual or perceived risk uncertainties associated with fetal exposure to pharmaceutical products may well lead sponsors, Institutional Review Boards, clinical investigators, and patients reluctant or unwilling to participate in such research, particularly in any studies in which there is not a clear and important potential therapeutic benefit to the participating pregnant women and/or her fetus

Additional General Comments

- The Introduction and Background sections should help frame the basis for conducting PK studies such as providing reference to relevant FDA and ICH guidance documents. For example, how does the Draft Guidance on conducting PK studies during pregnancy relate to the *Reviewer Guidance: Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities* (October 2001)? There are no aspects of the guidance document that relates to the nonclinical assessment of teratogenic and reproductive toxicity studies. Since there is an elaborate classification system for the data from these studies, it seems appropriate that research to be conducted in pregnant women would be to some degree affected by the classification of these nonclinical data. These classifications might limit the number or type of individuals that should become research participants, may affect the gestational stage in which human studies should be

proposed, and may affect when studies would be recommended during the registration or commercialization phases of drug development.

- The proposed basis for pregnancy PK studies in the Draft Guidance applies to most drugs and is not limited to therapeutic need. However, there are serious risk-benefit and ethical considerations involved in any non-therapeutic investigational drug studies in pregnant women due to concerns about unanticipated effects on the woman's pregnancy and her fetus. Statements relative to PK studies in renal and hepatic disease (lines 102-106) inappropriately equate these medical diseases with PK evaluations in healthy women who are pregnant.

  As there are many more issues associated with conducting clinical trials in pregnant women than conducting trials in other special populations, Lilly recommends generalizing the statements and not emphasizing specific diseases.

- Studies of drugs that have not passed the test of widespread post-registration clinical use may pose, or may possibly pose, greater risk than widely used medications that have withstood broad commercial use. The extent of prior clinical experience with a drug is an important component of the clinician's ability to counsel potential study participants about the perceived benefit – to risk of the trial. Furthermore, prior commercial experience with the drug will facilitate assessing causality in study participants who subsequently experience adverse birth outcomes. Unless the study drug is intended for use in pregnant women, studies of this type should be deferred until after a substantial period of post-marketing safety surveillance has occurred.

  Lilly recommends that PK studies in pregnant women to derive non-therapeutic data should not be considered unless the safety profile has been well characterized by post-marketing experience.

- If dose adjustment due to pregnancy is required, with few exceptions, the physiological changes of pregnancy are likely to require dosage increase, and the range of studies performed in biopharmaceutical packages, including "supratherapeutic exposure" in QTc and early dose-ranging studies may cover the range of exposure that could potentially occur in situations of pregnancy.

  The Agency's guidance should emphasize using all available data to predict when a dosage adjustment is likely to be needed in a pregnant woman.

- Many physiologic parameters in pregnancy (cardiac output, body mass, body composition, renal tubular filtration, P450 enzyme modulation) lie within the range of those observed in the general population of non-pregnant women and men. Extensive classical and population PK studies performed during drug development may serve to identify variables with significant impact on drug exposure.

  Lilly recommends that FDA's guidance emphasize that semi-quantitative predictions of the need for dose adjustment may be made on the basis of these analyses, which (in contrast to a pregnancy PK study) are likely to be available at the time of registration.

- For drugs that are dosed to clinical effect or therapeutic concentration, dosing guidance based on extrapolation from a small PK study may not be superior to clinically-directed dose optimization for drugs with a readily monitorable therapeutic effect or target concentration.

- Proving or establishing "no difference" is often more difficult than characterizing a large change. It would be appropriate if the guidance provides recommendations on ways to limit the number of participants exposed to the drug when "no difference" is an expected outcome. In the situation of an extensive understanding of the PK and PD properties of a drug, an underpowered study that only seeks to confirm the lack of major PK or PD differences would be a substantial advancement. If pregnancy PK or PD studies need to be powered to achieve a result that is robust and establish conclusively that there is no difference, the number of participants may be very large, and the results may turn out to be nothing short of a confirmation of prior knowledge. The important question that should precede the research is "how much would the PK or PD effects need to change before there would be a need to offset these changes by appropriate dosage adjustment".

  Lilly recommends the Agency provide clearer guidance on the use of a "no difference" based on statistical power versus a clinical effect.

- If data in pregnant women are needed, Lilly believes consideration should be given to initially assess the most perturbed physiologic state of pregnancy (e.g., early third trimester) to determine if pregnancy is associated with a clinically important change in the drug's PK, PD or safety profile. Absence of a clinically important effect when physiologic changes are greatest should reflect a similar absence of effect during earlier gestational and postpartum periods.

Specific Comments in the Draft Guidance:

Section II

Line 95 **Issue:** The guidance document indicates that a decrease in the concentration of albumin associated with pregnancy may lead to reduced protein binding, thereby affecting the drug's PK or PD. As noted by Benet (2002), with specific exceptions, alterations in protein binding do not contribute to changes in steady-state free drug concentration. Protein binding may be significant for low therapeutic index drugs with low clearance and small volume of distribution, but this scenario is uncommon.

Recommendation: Protein-binding alterations should not be presented as a risk for increased exposure to free drug. An exception may be made for drugs with low therapeutic index drugs and acute pharmacological effects that demonstrate low clearance and a small volume of distribution.

Section IV

Line 180 **Issue:** The proposal to study drugs pre-pregnancy is impractical. Postpartum studies are really the only realistic possibility for comparison to PK studies during pregnancy. Population PK models may also be a realistic substitute.

Recommendation: Acknowledge the impracticality of pre-pregnancy baseline studies.

Line 212 **Issue:** The proposal for narrow time windows in the 2nd and 3rd trimester is not workable in light of the difficulty in recruitment for these studies. In light of the continuous nature of physiological changes in pregnancy, the use of narrowly defined time windows is not warranted.

Recommendation: Proposed study design should permit enrollment of subjects at any time during the 2nd or 3rd trimester. Secondary analyses may be performed regarding the significance of changes at different times of pregnancy.

Section V, C

Line 307 **Issue** (see also Section VI, Line 431): For most medications the clinically available dose strength increments would be known at the time of a pregnancy study. A dose-adjustment recommendation would require a mean PK effect large enough that a different dose-strength (or dose interval) would better achieve the optimal drug exposure. For drugs that are available in 50-100% dose increments, dose adjustments would not be used if mean PK effects do not exceed 25-50%, respectively. The statistical paradigm used to demonstrate bioequivalence is not appropriate when significant differences between treatment conditions are expected.

Recommendation: The statistical approach should emphasize accurate description of mean changes in drug exposure. The study should have adequate power to detect a mean effect that would support a change in dose strength or dose interval. This criterion may be derived from available dose size or dose interval options. The known PK variability in non-pregnant subjects may be used for power analysis.

Section V, E

Line 352 **Issue:** As mentioned above, with few exceptions, steady-state free drug concentrations are not affected by protein binding. Protein binding in pregnancy may limit the ability to compare total drug concentrations in pregnant and non-pregnant populations. Nonetheless, the clinical benefit of free drug assay methodology would be limited to low Therapeutic Index drugs with potential for toxic effects prior to steady state equilibration with distribution and clearance processes (e.g. short-acting intravenous anti-arrhythmic.)

Recommendation: Measurement of individual protein binding should not be required except in those rare cases noted by Benet (2002). Exploratory analyses of free vs. total drug concentrations may be based on *in vitro* studies of the concentration dependency of protein binding.

Section V, F

Line 358 **Issue:** It is unknown whether drugs constitute a low risk for some subgroup. For example, a fetus may be at risk in ways that cannot be defined, especially for innovative drugs. The fetus could be considered a vulnerable subgroup in studies for these purposes and poses ethics and risk-benefit issues.

Recommendation: The guidance does not adequately discuss the long-term safety issues related to follow-up of the mothers and infants that are exposed during these studies. These issues should be addressed and are also a strong argument against performing studies outlined.

Line 359 **Issue:** The risk of retrospectively perceived harm from a participant taking an investigational agent during pregnancy is unrelated to the known toxicology or pharmacology of the drug.

Recommendation: Even with non-clinical data that demonstrate no organ toxicity, non-therapeutic trials in pregnant women should only even be considered after substantial post-marketing safety data has accrued.

Section VII

Line 460 **Issue:** In cases where pregnancy PK studies are not completed, or are not feasible, the known effects of increased cardiac output, body mass, renal tubular filtration, and CYP450 metabolism may contribute to presumptive guidance in pregnancy.

Recommendation: If significant effects of cardiac output, renal tubular filtration, body mass and composition on drug exposure have been studied in non-pregnant subjects, these should be extrapolated to predict the extent of changes typically seen in pregnant women. Lack of effect of these parameters may also be stated.

Line 465 **Issue:** Label statements about protein binding are misinterpreted by prescribing clinicians who assume that steady-state free drug concentrations may be increased.

Recommendation: Statement about protein binding should not be included in the label.

Again, we appreciate the opportunity to comment on the details of the proposed PK in Pregnancy Guidance.
Sincerely,

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